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(54) Title: NOVEL MEDICINAL HERBAL COMPOSITION FOR TREATING LIVER DISEASES AND HIV

(57) Abstract: The present invention provides a herbal pharmaceutical composition for treating patients with liver diseases and/or HIV. The composition contains fifteen (15) ingredients, which are diffuse hedyotis, bistort rhizome, giant knotweed rhizome, Asiatic moonseed rhizome, baical skullcap root, bovine biliary powder, milkvetch root, barbary wolfberry fruit, sanqi, red ginseng, figwort root, Chinese magnoliavine fruit, turmeric root-tuber, hawthorn fruit, and Chinese angelica. Among the fifteen (15) ingredients, diffuse hedyotis, bistort rhizome, giant knotweed rhizome, and Chinese magnoliavine fruit are the required herbs which contribute to the efficacy of the pharmaceutical composition.

NOVEL MEDICINAL HERBAL COMPOSITION FOR TREATING LIVER DISEASES AND HIV

FIELD OF THE INVENTION

5 The present invention relates to a novel herbal pharmaceutical composition and its use for treating patients with liver diseases (e.g., viral hepatitis [such as Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, and Hepatitis E], alcoholic or fatty liver, liver cirrhosis, and liver cancer) and HIV. The major ingredients in the herbal composition are diffuse hedyotis, bistort rhizome, giant knotweed rhizome, and Chinese magnoliavine fruit. The composition
10 further contains Asiatic moonseed rhizome, baical skullcap root, bovine biliary powder, tumeric root-tuber, hawthorn fruit; sanqi, barberry wolfberry fruit, red ginseng, figwort root, Chinese angelica, and milkvetch root. The present invention also relates to a method for making the medicinal herbal composition and methods for treating patients with the medicinal herbal composition.

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DESCRIPTION OF THE RELATED ART

Liver diseases have great impact on human health. Hepatitis is a kind of liver diseases, which is caused by liver inflammation due to infection of a variety of pathogens, which include, but are not limited to, viruses, bacteria, fungi, and protozoa. Hepatitis can be
20 categorized as acute, chronic, or fulminant.

Viral hepatitis is an enterically transmitted liver disease due to viral infection. The major transmission means for viral hepatitis is through ingestion. Viral hepatitis can also be transmitted through blood transfusion or similar means of hepatitis-virus-carrying blood or blood product such as blood plasma. Viral hepatitis is widespread around the world. For
25 example, there are approximately thirty million (30,000,000) viral hepatitis patients in China including an estimated number of nine million (9,000,000) new patients each year, and about one hundred million (100,000,000) hepatitis B virus (HBV) carriers. It is estimated that 10% of the pregnant women in China are HBV carriers. About one hundred thousand (100,000) people in China die of liver cancer originated as liver diseases each year.

30 Depending on the major etiologic agent, viral hepatitis is categorized into Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, and Hepatitis E. Hepatitis A is caused by hepatitis A virus (HAV); Hepatitis A can affect anyone and occur in isolated cases as well as widespread epidemics. Hepatitis B is a serious disease caused by hepatitis B virus (HBV). HBV attacks the liver and can cause lifelong infection, cirrhosis (scarring) of the liver, liver cancer, liver

failure, and death. Hepatitis C is caused by hepatitis C virus (HCV). Hepatitis D is caused by the hepatitis D virus (HDV) which is a defective single-stranded RNA virus that requires the helper function of HBV to replicate and to synthesize envelope protein composed of HBsAg to encapsulate HDV's genome. Hepatitis E is caused by hepatitis E virus (HEV), which is an etiologic agent of enterically transmitted non-A, non-B hepatitis. HEV is a spherical, non-enveloped, single-stranded RNA virus of approximately 32 to 34 nm in diameter. HEV has been provisionally classified in the *Caliciviridae* family; however, the organization of the HEV genome is substantially different from that of other Caliciviruses, and HEV may eventually be classified in a separate family.

The most common types of viral hepatitis are Hepatitis A, Hepatitis B, Hepatitis C, and Hepatitis E, which have similar major symptoms including decreased appetite, nausea, unease upper abdomen, lack of strength, etc. Acute jaundice is also one of the common symptoms. Chronic hepatitis is very difficult to cure. Severe hepatitis often comes on quickly and results in high mortality.

Traditional Chinese herbal compositions have been developed and shown success for preventing and treating various liver diseases. The types of traditional Chinese herbal medicine for treating hepatitis include medications having single or multiple herbal components and medications made of active ingredients extracted from the herbs.

For example, Qianglining injection solution is made of glycyrrhizic acid extracted from licorice (*Glycyrrhiza*). Glycyrrhizic acid reacts with ammonia to form a water-soluble ammonium salt of glycyrrhizic acid, which then can compound with amino acids. The injection solution is useful for treating chronic viral hepatitis, liver cirrhosis, and hepatoma. The total effective rate of qianglining injection solution is about 87.5%, in which 64.1% is significant, according to clinical studies conducted on hepatitis patients provided by Shanghai Huashan Hospital, Shanghai, China.

Yanhuanglian injection solution is derived from ground herb Yanhuanglian grown in Guangxi Province in China. The solution is useful for treating various types of hepatitis, liver cirrhosis, and liver cancer, with a reported clinical efficacy rate of 81.47%. The solution has an effective rate of 93.88% in cases involving acute jaundice patients, 87.50% in non-jaundice type hepatitis patients, 87.09% in chronic active type hepatitis patients, 69.23% in prolonged type hepatitis patients, and 80.95% in chronic cirrhosis patients. However, only 17.91% of the patients show changes of HBV surface antigen from positive to negative.

Shandougen (*Radix Sophorae Tonkinensis*) injection solution is useful for both acute and chronic viral hepatitis, and especially effective for chronic active hepatitis. As studied by Guangxi Medical College in Guangxi province, China, the total effective rate is 91.79% for chronic active hepatitis patients, and the substantial effective rate is 54.23%. Also, 64.93% of the patients' glutamate-pyruvate transaminase (GPT) level returns to normal in two (2) months after the treatment. However, some patients show recurring symptoms of hepatitis after the treatment is discontinued.

Umbellate pore fungus (*Polyporus umbellata*) injection solution has functions of improving immune function, inhibiting tumor, lowering level of transaminase, and inhibiting replication of hepatitis virus. After treating patients with chronic viral hepatitis with umbellate pore fungus injection solution, 35.6% of the patients return to normal serum GPT (SGPT) level, 76.61% of the patients show some lowering effects on transaminase level, 38.6% of the patients show HBV E antigen turning negative, and 13.1% of the patients show surface antigen turning negative.

Qidun fruit acid tablet has a total effective rate of 94.4% in patients with acute jaundice-type hepatitis. The total recovery rate is 64.8%. Qidun fruit acid tablet also shows an effective rate of 69.8% in chronic active hepatitis, in which 43.7% of the patients show a significant effect. The rate for HBsAg positive turning negative is 16.8%.

Gandezhi (Liver-curing) capsule has Wuren alcohol, *scutellarin*, mulberry fruit-spike (*Fructus Mori Albae*), salvia root (*Radix Salviae Miltiorrhizae*), and licorice (*Radix Glycyrrhizae Uralensis*) and is useful for lowering transaminase level. It has an effective rate of 80.0% for treating prolonged hepatitis and chronic hepatitis, according to studies reported by Guangzhou Zhongshan Medical College Hospital in China. There has been no report which shows that Gandzhi has effect on HBV Antigen turning negative.

Danggui (Chinese angelica root) pill is made of Chinese angelica root (*Radix Angelicae Sinensis*) and licorice (*Radix Glycyrrhizae Uralensis*). In a study conducted by Beijing Medical College in China, Danggui pill is effective for treating prolonged hepatitis (with an effective rate of 84.4%), chronic hepatitis (with an effective rate of 79.1%), and cirrhosis resulted from hepatitis (with an effective rate of 73.6%).

Hugang (liver-protecting) tablet is made from schisandra fruit (*Fructus Schisandrae Chinensis*) alcohol extractant, liver-protecting extractant (including Junchen, Zihu, and woad root (isatis root, *Radix Isatidis seu Baphicacanthi*)), and biliary powder, etc. It has an

effective rate of 95.08% for treating chronic hepatitis (70% with significant effect), and 82.5% for treating cirrhosis (63% with significant effect).

Jigu ("chicken bone") grass pill is made of Jigu grass, billiary powder, and bovine bezoar (*Calculus Bovis*). As studied by Beijing Children's Hospital in China, Jigu grass pill
 5 has a total effective rate of 100% in patients with acute viral hepatitis, 73.3% in patients with chronic active hepatitis, 70.4% in patients with chronic prolonged type hepatitis. However, Jigu grass pill does not appear to have any effect on other types of prolonged hepatitis.

Wuzi ("five ester") capsule is made from schisandra fruit (*Fructus Schisandrae Chinensis*) alcohol extractant. It shows function of lowering GPT level and is useful for
 10 treating chronic prolonged hepatitis. The total effective rate of wuzi capsule is 95.33%, in which 74.21% is significant.

Ganfuneng (liver-healing) formula contains *astragalus* (*Radix astragali membranaceus*), hawthorn fruit (*Fructus crataegi*), pueraria (*Radix puerariae*), Cornu Bubali powder, San-qi, etc. It has an effective rate of 88.7% for chronic hepatitis patients and 79.1%
 15 for GPT recovery.

Biyansha Hepatitis B-curing formulation is made from diffuse hedyotis (*Hedyotis diffusa* Willd.), rubia root (*Radix Rubiae Cordifoliae*), Indigo Pulverata Levis, glabrous greenbrier rhizome (*Rhizoma Smilacis Glabrae*), salvia root (*Radix Salviae Miltiorrhizae*), finger citron fruit (*Fructus Citri Sarcodactylis*), hawthorn fruit (*Fructus Crataegi*),
 20 Ganoderma Lucidum, Ophiopogon tuber (*Tuber Ophiopogonis Japonici*), and silkworm feces (*Excrementum Bombycis Mori*). The formulation has been used for treating infectious HBV, acute and chronic hepatitis, early-stage cirrhosis, swollen liver and spleen, etc. It has a total effective rate of 84.75% and an HBsAg turning negative rate of 41.35%, as shown in the study of 314 HBV patients at Xian Medical University Second Affiliated Hospital in China.

25 Ganpikang ("liver-spleen" health) capsule contains fourteen (14) herbal components including bupleurum (*Radix Bupleuri*), San-qi, and bear gallbladder (*Vesica Fellea Ursi*) powder. It has a curing rate of 53.33% and an effective rate of 40.0 for chronic active HBV, and a curing rate of 63.33% and an effective rate of 26.67 for chronic prolonged HBV.

Ruanjianhugan ("liver-protecting") tablet contains sophora root (*Radix Sophorae Tonkinensis*), prunella (*Spica Prunellae Vulgaris*), bushy knotweed root and rhizome (*Radix et Rhizoma Polygoni Cuspidati*), scutellaria (*Radix Scutellariae Baicalensis*), salvia root (*Radix Salviae Miltiorrhizae*), astragalus (*Radix Astragali Membranaceus*), ligustrum (*Fructus Ligustri Lucidi*), cardamon (*Fructus Amomi*), and hawthorn fruit (*Fructus Crataegi*).

It shows that 78% of the patients having HBeAg turned negative, 28-57% of the patients having HBsAg turned negative.

However, despite the effectiveness of the above herbal medicinal compositions in treating hepatitis, none of these compositions demonstrates significant effects on HBV antigen turning negative.

The present invention provides a novel pharmaceutical composition for treating liver diseases, particularly for treating patients with viral hepatitis (e.g., HAV, HBV, HCV and HEV), alcoholic or fatty liver, and liver cancer. The compositions described in the present invention also demonstrates significant clinical effects on patients with HIV. This composition is a natural Chinese medicine with little or no side effects and has no toxicity.

SUMMARY OF THE INVENTION.

The novel medicinal composition of the present invention comprises herb extracts from diffuse hedyotis, giant knotweed rhizome, bistort rhizome, Asiatic moonseed rhizome, baical skullcap root, bovine biliary powder, milkvetch root, barbary wolfberry fruit, sanqi, red ginseng, figwort root, Chinese magnoliavine fruit, turmeric root-tuber, hawthorn fruit, and Chinese angelica. The composition is effective in treating patients with liver diseases, including, but not limited to, viral hepatitis (e.g., HAV, HBV, and HCV, and HEV), alcoholic or fatty liver, liver cirrhosis and liver cancer. It is also effective for treating patients with HIV.

Among the herbs used in the composition, diffuse hedyotis, bistort rhizome, giant knotweed rhizome, and Chinese magnoliavine fruit are the necessary ingredients that provide for the efficacy of the composition. Asiatic moonseed rhizome, baical skullcap root, bovine biliary powder, tumeric root-tuber, hawthorn fruit, and sanqi are used mainly to improve or enhance the flavour, toning, and medicinal effects of, and to balance the excessive effects cause by diffuse hedyotis, bistort rhizome, giant knotweed rhizome, and Chinese magnoliavine fruit. In addition, barbary wolfberry fruit, red ginseng, figwort root, Chinese angelica and milkvetch root can be added to the composition to provide further nutrition to the liver during the recovery stage.

The weight ratio of diffuse hedyotis, bistort rhizome, giant knotweed rhizome, and Chinese magnoliavine fruit is preferred to be about 3: 3: 1: 2. The weight ratio of diffuse hedyotis, bistort rhizome, giant knotweed rhizome, Chinese magnoliavine fruit, asiatic moonseed rhizome, baical skullcap root, bovine biliary powder, tumeric root-tuber, hawthorn

fruit, and sanqi is preferred to be about 3: 3: 1: 2: 1: 1: 0.1: 1: 2: 1. The weight ratio of diffuse hedyotis, bistort rhizome, giant knotweed rhizome, Chinese magnoliavine fruit, asiatic moonseed rhizome, baical skullcap root, bovine biliary powder, tumeric root-tuber, hawthorn fruit, sanqi, barbary wolfberry fruit, red ginseng, figwort root, Chinese angelica, and
 5 milkvetch root is preferred to be about 3: 3: 1: 2: 1: 1: 0.1: 1: 2: 1: 3: 1: 2: 1: 3.

The present invention also provides a method for preparing the herbal pharmaceutical composition, which comprises the steps of: (1) grinding and mixing the entire plant of diffuse hedyotis, the dried rhizome of bistort rhizome, the dried rhizome of giant knotweed rhizome, and the dried ripe fruit of Chinese magnoliavine fruit to form a herbal mixture; (2) boiling the
 10 herbal mixture in water in two times (first by boiling the mixture in water for 2 hours, then, after the mixture has cooled down, boiling the mixture again for 1.5 hours); (3) filtering the boiled herbal mixture to separate the herbs from the herbal solution; (4) concentrating the herbal solution (preferably concentrating from about 1.4 fold by volume to about 1 fold by volume); and (5) spray-drying and granulating the concentrated herbal solution into granules,
 15 which can be further encapsulated.

DETAILED DESCRIPTION OF THE INVENTION

Traditional Chinese medicine has been in existence for more than two thousand years. It has a proven record of success for curing many kinds of diseases. Traditional Chinese
 20 medicine utilizes a variety of herbs and natural substances. Each herb/natural substance has its unique characteristics. By combining and balancing the unique characteristics of herbs, a doctor can prescribe a formulation with enhanced medicinal activities and with less or no toxicity by synergizing the medicinal effects among various herbs, while in the meantime, cancelling out or neutralizing the toxic effects of the herbs.

25 This, in Chinese herbal medicine, is regarded as to regulate between negative/hypoactive characteristics ("yin") and positive/hyperactive characteristics ("yang"). Under the definitions set forth in the traditional Chinese medicine, "yin" is defined as drugs which cure cold syndrome (which itself has hot or warm property), and "yang" is defined as drugs which cure heat syndrome (which itself has cold or cool property).

30 The pharmaceutical combination of the present invention comprises fifteen (15) ingredients, in which four (4) ingredients are the core ingredients which contribute to the primary efficacy and healing effect of the composition. They are: (1) diffuse hedyotis/spreading hedyotis (Pharmaceutical name: *Herba Hedyotidis diffusae*; Botanical

name: *Hedyotis diffusa* Willd.); (2) bistort rhizome (Pharmaceutical name: *Rhizoma Bistortae*; Botanical name: *Polygonum bistorta* L.); (3) giant knotweed rhizome (Pharmaceutical name: *Rhizoma Polygoni Cuspidati*; Botanical name: *Polygonum cuspidatum* Sieb. et Zucc.), and (4) Chinese magnoliavine fruit (Pharmaceutical name: *Fructus Schisandrae Chinensis*; Botanical name: *Schisandra chinensis* (Turcz.) Baill., S. spheanthra Rehd. et Wils.). The core ingredients are functioned in clearing heat and toxic substances while improving immune system and circulation, curing symptoms of jaundice, and having beneficial effect on internal organs.

There are six (6) additional ingredients that are used to improve and balance the pharmaceutical activities produced by the above named core ingredients. These six ingredients also have toning effect and can improve blood circulation in the liver. These six ingredients are: (1) Asiatic moonseed rhizome (Pharmaceutical name: *Rhizoma Menispermii*; Botanical name: *Menispermum dauricum* DC); (2) baical skullcap root (Pharmaceutical name: *Radix Scutellariae*; Botanical name: *Scutellaria baicalensis* Georgi); (3) bovine biliary powder (Zoological name: *Vesica Fellea Bovus*); (4) tumeric root-tuber (Pharmaceutical name: *Radix Curcumae*; Botanical name: *Curcuma wenyujin* Y.H. Lee et Cl Ling); (5) Hawthorn Fruit (Pharmaceutical name: *Fructus Crataegi*; Botanical name: *Crataegus pinnatifida* Bge.); and (6) sanqui (Pharmaceutical name: *Radix Notoginseng*; Botanical name: *Panax notoginseng* (Burk.)).

Finally, there are additional five (5) ingredients which are used to primarily provide nutrients and energy sources for patients so as to expedite the recovery process. These ingredients include: (1) barbary wolfberry fruit (Pharmaceutical name: *Fructus Lycii*; Botanical name: *Lycium barbarum* L.); (3) figwort root (Pharmaceutical name: *Radix Scrophulariae*; Botanical name: *Scrophularia ningpoensis*); (4) Chinese angelica (Pharmaceutical name: *Radix Angelicae sinensis*; Botanical name: *Angelica sinensis* (Oliv.) Diels); and (5) milkvetch root (Pharmaceutical name: *Radix Astragali*; Botanical name: *Astragalus membranaceus* (Fisch.) Bge.). Among these ingredients, red ginseng (*Radix Ginseng Rubra*) and milkvetch root (*Radix Astragali*) also have the capacity of improving immunological functions of the body to fend off diseases.

The pharmaceutical names, botanical or zoological names, family names, common descriptions, and major ingredients of the herbs used in the present invention is shown in Table 1.

Table 1. Herbs of the Present Pharmaceutical Composition

Pharmaceutical Name	Botanical /Zoological Name	Family	Common Description	Major Ingredients
<i>Herba Hedysotis Diffusae</i>	<i>Hedysotis diffusa</i> (Willd.) Roxb., also known as <i>Oldenlandia diffusa</i>	<i>Rubiaceae</i>	heydyotis, oldenlandia	hentriacontane, stigmastatrienol, ursolic acid, oleanolic acid, β -sitosterol, <i>p</i> -coumaric, β -sitosterol-D-glucoside
<i>Radix et Rhizoma Polygoni Cuspidati</i>	<i>Polygonum cuspidatum</i> Sieb. et Zucc.	<i>Polygonaceae</i>	Giant Knotweed root and Rhizome	emodin, chryso-phenol, rheic acid, emodin monomethyl ether, polygonin, and physcion-8- β -D-glucoside
<i>Rhizoma Bistortae</i>	<i>Polygonum bistorta</i> L.	<i>Polygonaceae</i>	Bistort Rhizome	n/a
<i>Rhizoma Menispermii</i>	<i>Menispermum dauricum</i> DC.	<i>Menispermaceae</i>	Asiatic Moonseed Rhizome	n/a
<i>Radix Scutellariae Baicalensis</i>	<i>Scutellaria baicalensis</i> Georgi	<i>Labiatae</i>	Baical Skullcap Root	baicalein, baicalin, wogonin, wogonoside, neobaicalein, oroxylin aglucuronide, camphesterol, β -sitosterol, benzoic acid
	<i>Vesica Fellea Bovus</i>		Bovine Biliary powder	n/a
<i>Radix Astragali</i>	<i>Astragalus membranaceus</i> (Fisch.) Bge. var. <i>mongholicus</i> . (Bge.) Hsiao or <i>Astragalus membranaceus</i> (Fisch.) Bge.	<i>Leguminosae</i>	Milkvetch Root	D- β -asparagine, 2', 4'-dihydroxy-5,6-dimethoxyisoflavane, calycosin, formononetin, cycloastragenol, astragalosides, choline, betaine, kumatakenin, sucrose, glucuronic acid, β -sitosterol

<i>Fructus Lycii</i>	<i>Lycium barbarum</i> L.	<i>Solanaceae</i>	Barbary Wolfberry Fruit	betaine, carotene, physalien, thiamine, riboflavin, vitamin C, β -sitosterol, linoleic acid
<i>Radix Notoginseng</i>	<i>Panax notoginseng</i> (Burk.) F.H. chen, <i>P. pseudoginseng</i> Wall, <i>P. sanchi</i> Hoo.	<i>Araliaceae</i>	San-chi, notoginseng, Tian qi, Shen san qi	Arasaponin A, arasaponin B, dencichine
<i>Radix Ginseng Rubra</i>	<i>Panax Ginseng</i> C.A. Mey	<i>Araliaceae</i>	Red Ginseng	Panaxatriol, Panaxadiol, Other Panoxisides, Panoquilon, Panaxin, Ginsenin, α -Panaxin, Protopanaxadiol, Protopanaxtriol, Panacene, Panaxynol, Panaenic Acid, Panose, Dammarane, Glucose, Fructose, Maltose, Sucrose, Nicrotinic Acid, Riboflavin, Thiamine
<i>Radix Scrophulariae Ningpoensis</i>	<i>Scrophularia ningpoensis</i> Hemsl. or <i>S. buergeriana</i> Miq.	<i>Scrophulariaceae</i>	Figwort Root, Scrophularia	l-asparagine, oleic acid, linoleic acid, stearic acid, carotene
<i>Fructus Schisandrae Chinensis</i>	<i>Schisandra chinensis</i> (Turcz.) Baill., <i>S. sphenanthera</i> Rehd. et Wils.	<i>Magnoliaceae</i>	Chinese Magnoliavine Fruit, schisandra fruit	sesquicarene, β -bisabolene, β -chamigrene, α -ylangene, schizandrin, pseudo- γ -schizandrin, deoxyschizandrin, schizandrol, citral, stigmastrol, vitamin C, vitamin E

<i>Tuber Curcumae</i>	<i>Curcuma wenyujin</i> Y. H. Lee et C. Ling., or <i>Curcuma Longa</i> L., or <i>Curcuma aromatica</i> Salisb., or <i>Curcuma zedoaria</i> Rosc., or <i>Curcuma kyangsiensis</i> S. G. Lee et C. F. Liang	<i>Zingiberaceae</i>	Turmeric Root-tuber, curcuma	d-camphene, d-camphor, 1- α -curcumene, 1- β -curcumene, curcumin, demethoxycurcumin, bisdemethoxycurcumin, turmerone, ar-turmerone, carvone, p-tolylmethylcarbionoldiferuloylmethane
<i>Fructus Crataegi</i>	<i>Crataegus pinnatifida</i> Bge.; <i>C. pinnatifida</i> Bge. var. major N.E. Br. or <i>C. suneata</i> Sieb. et Zucc.	<i>Rosaceae</i>	Hawthorn Fruit	crategolic acid, citric acid, tartaric acid, flavone, sugars, glycosides, vitamin C
<i>Radix Angelicae Sinensis</i>	<i>Angelica sinensis</i> (Oliv.) Diels	<i>Umbelliferae</i>	Chinese Angelica root, tang-kuei	butylidene phthalide, ligustilide, n-butylidene-phthalide, sesquiterpenes, carvacrol, dihydrophthalic anhydride, sucrose, vitamin B ₁₂ , carotene, β -sitosterol

Diffuse hedyotis or spreading hedyotis (*Herba Hedyotidis Diffusae*) belongs to the family of *Rubiaceae*. The entire plant is used as an herbal medicinal component. The herb has no toxicity. The herb is harvested in summer and autumn in mainland China and in late spring or early winter in Taiwan. In "Materia Medica" (Chinese Herbal medicine), compiled and translated by Dan Bensky & Andrew Gamble, diffuse hedyotidis clears heat and resolves dampness by promoting urination. It is particularly useful for relieving hot painful urinary dysfunction and damp-heat jaundice. Diffuse hedyotidis is the major ingredient in the present herbal pharmaceutical composition which contributes to the medicinal effect on liver diseases and HIV.

Bistort rhizome (*Rhizoma Bistortae*) is the dried rhizome of the plant *Polygonum bistorta* L. It belongs to the family of *Polygonaceae*. Bistort rhizome has moderate cool

property (meaning that bistor rhizome is an "yang" herb). It can be used to remove toxic heat, to promote the subsidence of swelling and to stop bleeding.

Giant knotweed rhizome (*Radix et Rhizoma Polygoni Cuspidati*) is the dried rhizome and root of *polygonum cuspidatum* Sieb. et Zucc. It belongs to the family of *Polygonaceae*.

- 5 The plant is grown throughout China, especially Jiangsu, Zhejiang, Anhui, Guangdong, Guangxi, Sichuan, and Guizhou provinces. The plant is harvested in spring and autumn. Giant knotweed rhizome is normally used to dispel damp, to eliminate blood stasis and alleviate pain, to relieve cough, and to resolve phlegm.

- Chinese magnoliavine fruit (*Fructus Schisandrae*) is the dried ripe fruit of *Schisandra chinensis* (Turcz.) Baill. or *Schisandra sphenanthera* Rehd. et Wils. It belongs to the family of *Magnoliaceae*. The former, the best of its kind, is produced in northern parts of China and is habitually called "Northern schisandra fruit"; the latter is commonly referred to as the "Southern schisandra fruit" as it is produced in the southern parts of China. Both kinds can be used for the pharmaceutical preparation of the present invention. The fruit is collected in
15 autumn and dried under the sun after removing the fruit stalks. Chinese magnoliavine fruit is generally used to arrest discharges, replenish qi, promote fluid secretion, tonify the kidney, and induce sedation. Chinese magnoliavine fruit can also decrease the level of GPT (glutamate-pyruvate transaminase) in patients with hepatitis.

- Asiatic moonseed rhizome (*Rhizoma Menispermī*) is the dried rhizome of
20 *Menispermum dauricum* DC. It belongs to the family of *Menispermaceae*. Asiatic moonseed rhizome has cool property. It can be used to remove toxic heat and relieve rheumatic pains.

- Baical skullcap root (*Radix Scutellariae*) is the dried root of *Scutellaria baicalensis georgi*. It belongs to the family of *Labiatae*. The plant is produced in the provinces of Hebei, Shanxi, Inner Mongolia, etc., and collected in spring or autumn. Baical skullcap root
25 is used to remove damp-heat, counteract toxicity, arrest bleeding, and prevent abortion, in patients.

Bovine biliary powder is the gallbladder of the cow, *Vesica Fellea Bovus*. It can clear heat and alleviate spasms.

- Turmeric root-tuber (*Radix Curcumae*) is the dried root tuber of *Curcuma wenyujin* Y. H. Lee et C. Ling., or *Curcuma Longa* L., or *Curcuma aromatica* Salisb., or *Curcuma zedouria* Rosc., or *Curcuma kwangsiensis* S. G. Lee et C. F. Liang. The herb is mainly
30 produced in Sichuan, Zhejiang, Guangdong, and Guangxi provinces in China, and harvested in winter or spring, washed clean after the removal of the hairy rootlets, boiled thoroughly.

and dried in the sun. It belongs to the family of *Zingiberaceae*. Turmeric root-tuber tastes bitter and had cool property. It can be used to clear heat, alleviate spasms and chest pain, and resolve phlegm.

Hawthorn fruit (*Fructus Crataegi*) is the dried ripe fruit of *Crataegus pinnatifida* Bge. var major N. E. Br., or *Crataegus pinnatifida* Bge., or *Crataegus cuneata* Sieb. It is produced primarily in Henan, Jiangsu, and Shandong provinces of China. It is harvested in autumn, sliced, and dried in sunlight. It belongs to the family of *Rosaceae*. Hawthorn fruit is normally used to stimulate digestion and promote the functional activity of the stomach. It can also improve the normal blood flow and dissipate blood stasis.

Sanqi, or San-chi, (*Radix Notoginseng*) belong to the family of *Araliaceae*. Sanchi (Sanqi) is the dried root of *Panax notoginseng* (Burk.) F. H. Chen. The plant is also known as *P. pseudoginseng* Wall and *P. sanchi* Hoo. The plant grows in Yunnan, Guangxi, Sichuan, Guizhou, and Jiangxi provinces of China, and is harvested in the autumn or winter of the third or seventh year, either before the flowers bloom (better) or after the fruit is ripe. H. Gao et al., Pharmaceutical Research, (1996) 13(8): 1196-1200, disclose that polysaccharides from *Panax notoginseng* (San-Chi) have immuno-stimulating activities *in vitro*.

Barbary wolfberry fruit (*Fructus Lycii*) is the dried ripe fruit of *Lycium barbarum* L. It belongs to the family of *Solanaceae*. The plant is mainly produced in Ningxia, Gansu, and Qinghai provinces of China. It is harvested in summer and autumn. It nourishes and tonifies the liver and kidneys. It can also replenish vital essence and improve eyesight.

Figwort Root (*Radix Scrophulariae*) is the dried root of *Scrophularia ningpoensis* Hemsl. It belongs to the family of *Scrophulariaceae*. The herb is chiefly produced in Zhejiang and Sichuan provinces of China and harvested in winter when the part of the plant above-ground has withered. The roots are piled and dried in sunlight alternately until the inside becomes black and then sliced for use. Figwort root can reduce heat from blood. It also has nourishing capacity and can counteract toxicity.

Red ginseng (*Radix Ginseng Rubra*) is the steamed and dried root of the cultivated form of *Panax ginseng* C. A. Mey (commonly known as "Yuanshen"). The herb turns red after being steamed and its properties become warmer in nature. It belongs to the family of *Araliaceae*. The pharmaceutical effects of ginseng is in its dried root. Ginseng has effects on central nervous system. It enhances both stimulatory and inhibitory processes in the central nervous system, thereby improving the adaptability of nervous responses. Ginseng can also

lower serum glucose and cholesterol. It also shows therapeutic and preventive effect on peptic ulcer.

Chinese angelica (*Radix Angelicae Sinensis*) is the dried root of *Angelica sinensis* (Oliv.) Diels. It belongs to the family of *Umbelliferae*. The herb is mainly produced in Gansu and Shanxi provinces of China. It is harvested in late autumn, smoked dry on slow fire after getting rid of the rootlets, sliced, or stir-baked with wine. Chinese angelica can enrich blood, promote blood circulation, regulate menstruation, relieve pain, and relax bowels.

Milkvetch root (*Radix Astragali*) is the dried root of *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus*. (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. It belongs to the family of *Leguminosae*. The herb is mainly produced in Shanxi, Gansu, Heilongjiang, and Inner Mongolia of China. The plant of four-year old or older is harvested in spring or autumn. Milkvetch root can promote discharge of pus and the growth of new tissue.

The herbal composition of the present invention was suitable for preparation in a scale typical for pharmaceutical industry as well as for smaller measure.

In the process for making the herbal composition of the present invention, the individual herbal components are pretreated according to the common procedures. The herbs are cut and put in a container with water to boil and simmer twice. The first time of simmering takes two hours, the solution is collected, and water is added for the second time of simmering for 1.5 hour. The solutions from the simmering steps are collected by passing through a sieve/filter. The filtrate is then condensed from about 1.4 fold by volume to 1.0 fold by volume. Subsequently, the liquid condensate is spray-dried and granulated to form particles. The particles are further packaged and preserved for use or for further analysis by the conventional means of the active ingredients to ensure their quality.

The composition of the present invention can further be processed and formulated in a form suitable for oral administration or intravenous injection.

The following example is illustrative, but not limiting the scope of the present invention. Reasonable variations, such as those occur to reasonable artisan, can be made herein without departing from the scope of the present invention.

EXAMPLE 1Pharmaceutical Preparation

The kinds and amounts of herbal ingredients used in the process of making the
 5 pharmaceutical composition of the present invention are described in Table 2.

Table 2. Ingredients Used In Example 1.

Component	Amount (g)	Component	Amount (g)
Diffuse heydyotis	90	Sanchi	30
Bistort Rhizome	90	Red Ginseng	30
Giant Knotweed root and Rhizome	30	Figwort root	60
Asiatic Moonseed Rhizome	30	Chinese Magnoliavine Fruit	60
Baical Skullcap Root	30	Turmeric Root-tuber	30
Bovine Biliary powder	3	Hawthorn fruit	60
Milkvetch Root	60	Chinese Angelica	30
Barbary Wolfberry Fruit	90		

The individual herbal components were pretreated according to common procedures. The herbs were weighed according to Table 2. The herbs were cut into small pieces and put
 10 in a container with water to boil and simmer twice, the first time for two hours, and the second for 1.5 hour. After the first simmering, solution was poured out and water was added to the container for the second simmering. The solutions from the two simmering steps were collected to pass through a sieve/filter, and then, condensed at a ratio of 1: 1.4. The liquid condensate was spray-dried and granulated to form particles. The particles were further
 15 packaged into about 1000 capsules. The capsules are called "Yi-Gan Kang capsules", abbreviated "YGK" capsules. The liquid condensate can also be made for intravenous injection. The injection solution is called "YGK" herbal injection solution. The herbal composition of the present invention is called "YGK" herbal composition.

EXAMPLE 2Efficacy of the YGK Herbal Composition on
Treatment of Patients with Hepatitis B (HBV)

5 The clinical research was conducted in the Liberty Military Hospital 211 in China. The course of hepatitis B is determined by many factors, including immune response, host genetic factors, and HBV mutations. The chronic hepatitis distinguishes from the acute hepatitis. The acute hepatitis is the active and symptomatic infection of the liver. A patient with the acute hepatitis is contagious. Symptoms of acute HBV infection are non-specific, but may include malaise, anorexia or jaundice. A chronic hepatitis patient is asymptomatic. 10 The HBV is present in the liver and blood, although there are usually no obvious physical symptoms. Specific blood tests will reveal the presence of the virus, and the patient is also contagious via blood, birth, sex, needles, etc. Cirrhosis is the pathological dysfunctional state of the liver, the hardening of the liver as the result of chronic hepatitis, chronic persistent 15 hepatitis (CPH) and chronic active hepatitis (CAH).

A total of 948 patients with acute HBV, chronic HBV, and liver cirrhosis participated in a clinical comparative study. The patients were divided into two (2) groups. The study group had 642 patients and the comparative group has 306 patients. The data on patients who participated in this study are listed in Table 3.

Table 3. Patients Data in the Clinical Study

Group	Study Group	Comparative Group
Total Number of Patients	642	306
Sex Distribution of the Patients	Male: 482 Female: 160	Male: 229 Female: 77
Age Distribution of Patients	7 to 74 years old (average age: 32.5)	8 to 70 years old (average age: 30.5)
*Symptoms of Patients' Liver Disease	Acute Hepatitis B: 282 Chronic Hepatitis: 276 Cirrhosis: 84	Acute Hepatitis B: 109 Chronic Hepatitis B: 114 Cirrhosis: 83

(* According to the diagnosis criteria of Hepatitis revised at the Shanghai Hepatitis Conference in 1980, Shanghai, China.)

The patients were treated according to the following regime:

(1) The patients in the study group were each orally administered eight (8) YGK herbal composition containing the herbal composition of the present invention per day.

(2) The patients in the comparative group were each orally administered four (4) Hugang ("liver protecting") tablets per day. A description of Hugang tablets has been provided in the "Background" section, *supra*.

The treatment lasts for ninety (90) days.

Table 4 shows the results of this clinical comparative study.

Table 4. Effects of YGK Capsule Treatment

Group	Number of Patients with Positive Effect* (%)
Study (642 patients)	456 (71.03%)
Comparative (306 patients)	104 (33.98%)

($p < 0.01$)

*: Positive effect means that the hepatitis B envelope antigen (HBeAg) and HBV DNA of the patients turn negative after taking the YGK herbal composition for 90 days.

As indicated in Table 4, approximately 71.03% of patients who took the YGK herbal composition for 90 days show positive responses to the herbal composition. This is contrary to the comparative group where the patients were given a popular "liver protecting" tablets which were available in the Chinese market. Patients who had taken the "liver protecting" tablets only have an effective rate of approximately 33.98% to show improvement in their liver diseases.

The Hepatitis B virus (HBV) consists of a surface and a core. The core contains a DNA polymerase and an e antigen. The DNA structure is double stranded and circular. HBV has four (4) genes encoding four (4) polypeptides: the S (surface), the C (core), the P (polymerase), and the X (transcriptional transactivating).

The S gene consists of three (3) regions, the pre-S1 region, the pre-S2 region, and the region that encodes the surface protein (HBsAg). Very rarely a mutation occurs in the S gene which aborts the production of HBsAg so that a person maybe HBsAg negative but still has the virus present as determined by HBV DNA. In addition, the HBsAg particles are antigenically complex and the antigenic determinants have been identified as one single

common determinant designated a, and four (4) major subdeterminants designated as d, y, w, and r. Thus, the four (4) major determinants are adw, adr, ayw, and ayr.

The C gene consists of two (2) regions, the pre-core region and the core region, which encodes for two different proteins, the core antigen (HBcAg), and the e antigen (HBeAg). A mutation in the pre-core region may stop the production of HBeAg, thus, a person may be HBeAg negative, but HBsAg positive and HBV DNA positive. Another type of mutant in the core region is called HBV2. The patients that have HBV2 mutant are HBsAg positive but lack HBeAg and HBV DNA.

Because of the complexity and the antigenic differences among the virus, there are a number of tests available for HBV including:

- (1) a test for HBsAg, which is an indicator of the presence of the HBV;
- (2) a test for HBeAg, which correlates with the viral replication and infectivity, it indicates a high amount of the virus in the blood, thus, is an indicator of the activity and infectivity of the HBV; and
- (3) a test for HBV DNA, which is an indication of the virus presence and activity.

Tables 5-7 indicated the change of Hepatitis B envelope Antigen ("HBeAg"), Hepatitis B surface antigen ("HBsAg"), hepatomegaly, and splenomegaly in the patients after the treatment.

Table 5. Effect of Herbal Composition on HBeAg in Patients

Group		Study Group	Comparative Group
Acute Hepatitis Patients	Number of Patients with HbeAg(+)	260	78
	Number of Patients with HbeAg(+) After Treatment	48	59
	Percentage of Patients With HbeAg Turning Negative	81.5%	24.36%

Chronic Hepatitis Patients	Number of HbeAg(+) Patients	206	82
	Number of HbeAg(+) Patients After Treatment	74	64
	Percentage of Patients With HbeAg Turning Negative	64.0%	21.95%
Cirrhosis Patients	Number of HbeAg(+) Patients	24	26
	Number of HbeAg(+) Patients After Treatment	14	22
	Percentage of Patients With HbeAg Turning Negative	41.7%	15.38%

As indicated in Table 5, the percentages of patients with HBeAg turning negative in all three (3) categories of patients (including acute hepatitis, chronic hepatitis, and cirrhosis) are 2.7-3.3 times higher than those of the comparative groups. This demonstrates that the YGK herbal composition had significant effect on HBeAg turning negative and inhibiting HBV activity and infectivity.

Table 6. Effect of Herbal Composition on HBsAg in Patients

Group		Study Group	Control Group
Acute Hepatitis Patients	Number of Patients with HbsAg(+)	262	84
	Number of Patients with HbsAg(+) After Treatment	116	73
	Percentage of Patients With HBsAg Turning Negative	55.7%	13.09%
Chronic Hepatitis Patients	Number of HbsAg(+) Patients	216	87
	Number of HbsAg(+) Patients After Treatment	118	78
	Percentage of Patients With HBsAg Turning Negative	45.37%	10.30%
Cirrhosis Patients	Number of HbsAg(+) Patients	64	43
	Number of HbsAg(+) Patients After Treatment	50	40
	Percentage of Patients With HBsAg Turning Negative	21.88%	6.98%

As indicated in Table 6, the percentages of patients with HBsAg turning negative in all three (3) categories of patients including acute hepatitis, chronic hepatitis, and cirrhosis were 3.1-4.4 times of those of the comparative groups. This demonstrates that the YGK herbal composition had significant effect on HBsAg turning negative and inhibiting the HBV.

- 5 In addition to HBeAg and HBsAg turning negative, the YGK herbal composition also show greater effects on increased appetite and decreased various symptoms of liver diseases than the comparative group using Hugang "liver protecting" tablets.

Table 7. Effect on Hepato-Splenomegaly

Group	Reduced Hepatomegaly	Reduced Splenomegaly
Study Group	79.72%	58.54%
Comparative Group	30%	28.8%

- 10 Hepatomegaly and splenomegaly are related to and possibly caused by viral infection. The reduced hepatomegaly and splenomegaly in patients was indicative to reduced symptoms of viral infection.

In summary, the YKG herbal composition demonstrates effect on treating patients with HBV, which including acute hepatitis B, chronic hepatitis B, and cirrhosis.

- 15 Example 3

Effects of the YGK Herbal composition on
Treatment of Patients with Chronic Hepatitis B (HBV)

- The clinical research was conducted in the Liberty Military 302 Hospital, Ninth Section, China. The research was conducted on treatment effects of the herbal composition
20 of the present invention on chronic hepatitis B patients.

- Chronic Hepatitis is an ongoing injury to the cells of the liver with inflammation which lasts for longer than six months. The causes of chronic hepatitis include: viruses, metabolic or immunologic abnormalities and medications. Symptoms resulted from the injury of hepatocytes, the inflammation or from the resulting scarring is called cirrhosis.
- 25 Chronic hepatitis may follow acute hepatitis B or C or may develop quietly without an acute illness. Liver biopsy is helpful in that it confirms the diagnosis, aids in establishing the cause (etiology) and can demonstrate the presence of cirrhosis. It is less helpful in judging the response to treatment. Approximately 25% patients with chronic hepatitis B will develop cirrhosis, causing permanent and serious liver damage. Chronic carriers of HBV are far more
30 likely to develop hepatocellular carcinoma than non-carriers.

It is believed that chronic infections develop as the result of a weak T helper (Th) cell response to the virus, in particular to the HBsAg. The T cell response is responsible for clearing the infected cells in the host's system. When the clearance is inefficient and the infected cells persist in the body, a chronic infection develops. As the HBsAg titer increases, the patient moves into acute, symptomatic disease. When the titer of anti-HBsAg rises, the symptoms of HBV begin to decline and patient reaches the immune state.

Chronic hepatitis has been divided into two categories based on histologic findings: chronic persistent hepatitis (CPH) and chronic active hepatitis (CAH). Characteristically, specimens from liver biopsy identified as CPH show inflammation confined to the portal triad (does not penetrate the limiting plate). Specimens identified as CAH show inflammation that penetrates the limiting plate, extending to the surrounding individual hepatocyte and yielding piecemeal necrosis. Under this schema, CAH eventually reaches a point where lobular architecture is destroyed, and bands of necrosis (bridging necrosis) are replaced by scar tissue (bridging fibrosis), resulting in the characteristic features of cirrhosis.

Sixty (60) patients with chronic hepatitis B are divided into two (2) groups, one group for treatment with YKG herbal composition and the other with Hugang ("Liver protecting") tablets. The study was conducted and maintained for three (3) months. The patients information in the two (2) groups are shown in Table 8:

Table 8. Compositions of the Patients in the Clinical Study

Group	Study Group	Comparative Group
Total Number of Patients	30	30
Sex Distribution of the Patients	Male: 26 Female: 4	Male: 25 Female: 5
Age Average Patients	32.8	35.1
Duration of Illness	2 months to 11 years	2 months to 9 years
*Symptoms of Patients' Liver Disease	CPH: 13 CAH: 17	CPH: 10 CAH: 20

* According to the diagnosis criteria of hepatitis revised at the Shanghai Hepatitis Conference in 1980.

Table 9 shows the changes in HBsAg, HBeAg, and HBV-DNA in patients after treatment with the YGK herbal composition (the study group) or Hugang tablets (the comparative group).

As indicated above, HBsAg can be detected in patients with acute infection as well as patients who are chronic HBV carriers. In the serological test, decreased titer of HBsAg indicates that the symptoms of HBV are lessened and the patient is approaching the immune state.

Table 9. The Changes of HBsAg, HBeAg, and HBV-DNA in Patients

Group	HbsAg		HbeAg		HBV-DNA Sero-Negative (%)	SGPT Recovery Rate(%)
	Sero-Negative (%)	Decreased Titer (%)	Sero-Negative (%)	Decreased Titer (%)		
Study Group	1/30 (3.33%)	6/30 (20.00%)	12/26 (46.15%)	6/26 (23.08%)	9/15 (60.00%)	73.33%
Comparative Group	0/30 (0%)	2/30 (6.67%)	5/27 (18.52%)	2/27 (7.41%)	4/18 (22.22%)	71.43%

$p < 0.05$.

As indicated in Table 9, the YGK herbal composition has significant effects on chronic hepatitis patients. Patients treated with the YGK herbal composition have Serum Glutamic Pyruvic Transaminase/Serum alanine aminotransferase (SGPT/ALT) recovery rate of 73.33%, HBeAg turning negative rate of 46.15%, HBV-DNA turning negative rate of 60.00%, suggesting that the YGK herbal composition has significant effects on inhibition of HBV replication and presence and depletion of aminotransferase. In addition, there was no toxic adverse reaction on the patients treated with the YGK herbal composition, according to clinical observation.

EXAMPLE 4

Case Studies on Effects of the YGK Herbal composition on Patients with Hepatitis B

The clinical research was conducted in the Contagious Disease Department of People's Liberation Army Hospital Branch 113 in China. The research was conducted on treatment effects of the YGK herbal composition on hepatitis B patients.

Each patient was tested for various markers. Serum alanine aminotransferase (ALT) is an enzyme appears in liver cells, with lesser amounts in the kidneys, heart, and skeletal muscles. When such damage occurs, ALT is released from the liver cells into the bloodstream, often before jaundice appears, resulting in abnormally high serum level of ALT that last for days or weeks. ALT is a relatively specific indicator of acute liver cell damage. Serum bilirubin (BIL) is also tested as an indication of liver diseases.

Case #1 was a twenty-four years old male patient with chronic hepatitis B, with general weakness for more than one year. Table 10 shows the diagnoses of patient *case #1* before and after treatment with the YGK herbal composition:

Table 10. Diagnoses of the Patient #1 Before and After the Treatment

	TBIL (nmol/L)	ALT (U/L)	HBsAg	HbsAb	HBeAg	HbeAb	HbcAg	HBcAb (IgM)	PCR HBV- DNA
Before Treatment	42	231	+	-	+	-	+	+	++
			(1:64)						
After Treatment	18.6	66	-	+	-	+	+	+	--

Table 10 indicates that the patient was in a state of immunity towards HBV and with alleviated infection as shown by the significant decrease of the viral DNA, and viral proteins, HBsAg, HBeAg, HBcAg, with increased amount of the antibodies against the viral protein in the serum.

Case #2 was a sixty-six years old male patient with recurrent abdominal fullness and general weakness for about ten (10) years with liver cirrhosis and splenomegaly. The following are the diagnoses of the patient before and after treatment with the YGK herbal composition (Table 11).

Table 11. Diagnoses of the Patient #2 Before and After
Treatment with the YGK herbal composition

	TBIL (nmol/L)	ALT (U/L)	HBsAg	HbsAb	HBcAg	HbeAb	HbcAg	HBcAb (IgM)	PCR HBV- DNA
Before Treatment	44.8	382	+	-	+	-	+	+	+++
			(1:64)						
After Treatment	25.3	43.8	+	-	-	+	+	-	+
			(1:32)						

Table 11 shows that patient #2 was in a state of alleviated infection symptoms towards HBV as shown by the significant decrease of viral DNA, and viral proteins. The data also show an increase in immunity as evidenced by reduced amount of HBsAg, HBcAg, HBcAg, and an increased amount of the antibodies against the viral proteins in the serum.

Case #3 was a thirty-one years old male patient with general weakness for more than one (1) month, treated in local Chinese Medicine clinic and subsequently hospitalized as acute biliary hepatitis B patient. The following are the diagnoses of the patient before and after treatment with the YGK herbal composition (Table 12).

Table 12. Diagnoses of the Patient #3 Before and After
the Treatment With the YGK Herbal composition

	TBIL (nmol/L)	ALT (U/L)	HBsAg	HbsAb	HBcAg	HbeAb	HbcAg	HBcAb (IgM)	PCR HBV- DNA
Before Treatment	154	520	+	-	+	-	+	+	+++
			(1:64)						
After Treatment	22.1	29.1	+	-	-	+	+	-	+
			(1:32)						

Table 12 shows that the patient was in a state of alleviated infection symptoms towards HBV as shown by the significant decrease of viral DNA, and viral proteins. The data also show an increase in immunity as evidenced by reduced amount of HBsAg, HBcAg, HBcAg, and an increased amount of the antibodies against the viral proteins in the serum.

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Case #4 was a forty-five years old male acute biliary hepatitis B patient with recurrent abdominal fullness, abdominal pain and general weakness for about one week. The following are the diagnoses of the patient before and after the treatment with the herbal composition of the present invention (Table 13).

5

Table 13. Diagnoses of the Patient #4 Before and After
the Treatment With the YGK Herbal composition

	TBIL (nmol/L)	ALT (U/L)	HBsAg	HbsAb	HBeAg	HbeAb	HBcAg	HBcAb (IgM)	PCR HBV- DNA
Before Treatment	143	966	+	+	+	-	+	+	++
			(1:64)						
After Treatment	15.3	42.1	+	-	-	+	+	-	--
			(1:32)						

Table 13 shows that the patient is in a state of alleviated infection symptoms towards HBV as shown by the significant decrease of viral DNA, and viral proteins. The data also show an increase in immunity as evidenced by reduced amount of HBsAg, HBeAg, HBcAg, and an increased amount of the antibodies against the viral proteins in the serum.

Case #5 was a thirty-one years old male acute biliary hepatitis B patient with abdominal fullness and general weakness for about five (5) days and then admitted. The following are the diagnoses of the patient before and after the treatment with the herbal composition of the present invention (Table 14).

15

Table 14. Diagnoses of the Patient #5 Before and After
Treatment With the YGK Herbal composition

	TBIL (nmol/L)	ALT (U/L)	HBsAg	HbsAb	HBeAg	HbeAb	HBcAg	HBcAb (IgM)	PCR HBV- DNA
Before Treatment	47.7	694	+	+	+	-	+	+	++
			(1:64)						
After Treatment	19.8	138	+	+	+	-	+	-	-
			(1:32)						

Table 14 shows that the patient is in a state of alleviated infection symptoms towards HBV as shown by the significant decrease of viral DNA, and viral proteins. The data also show an increase in immunity as evidenced by reduced amount of HBsAg, HBeAg, HBcAg, and an increased amount of the antibodies against the viral proteins in the serum.

5 Table 15 shows the percentage of patients with therapeutic effects in different markers.

Table 15. Therapeutic Effects on Patients After
Treatment with the YGK Herbal composition

<u>Therapeutic Effects</u>	<u>Percentage of Patients*</u>
Obvious therapeutic effects	80.9%
Improved therapeutic effects	19.10%
Hepatomegaly	75%
Splenomegaly	62.5%
<u>Normalization of liver function</u>	
ALT	93.7%
Bilirubin	91.1%
<u>Seroconversion</u>	
HBsAg(+) to HbsAg (-)	33.3%
HBsAb(-) to HbsAb (+)	23.8%
HbeAg(+) to HbeAg (-)	68.6%
HbeAb(-) to HbeAb (+)	23.9%
HBcAb(+) to HbsAb (-)	43%
HBV-DNA(+) to HBV-DNA(-)	39.5%

10 * The study included a total number of 42 patients (male: 31; female: 11), who were aged between 16 and 63 (average age: 42). Before treatment, twenty six (26) of the patients were diagnosed with acute hepatitis B, eight (8) with chronic hepatitis B; and eight (8) with chronic active hepatitis B. Thirty eight (38) patients had abnormal serum ALT. Thirty four (34) patients had abnormal serum BIL. Forty two (42) patients had HBV Marker (positive +). Thirty eight (38) patients had HBV-DNA as tested by PCR (positive +). Thirty five (35)
15 patients were HBeAg positive. Thirty two (32) patients were anti-HAV, anti-HCV, anti-HEV.

Results: The patients after being treated with the YGK herbal composition showed improvement of subjective symptoms, especially pain on liver area, fast normalization of liver function. Their ALT levels started to fall in about sixteen (16) days generally. Possible anti-viral activity was shown in the patients: the rate of HBeAg turning negative was commonly found in the YGK herbal composition treated patients (68.6%). No side-effects were noted in the treated patients.

EXAMPLE 5

Effects of the YGK Herbal Composition On Animals With Liver Diseases

The animal study was conducted at Korean Central Research Center.

10

Experiment 5.1: Analysis of Effect on Alcoholic or Fatty Liver in White Rats

Purpose: The experiment was conducted to investigate effects of the herbal composition on alcohol metabolism in white rats, especially, the influence on the ability to transform alcohol to triglyceride and cholesterol. The experimental dosage was 1 g/kg.

15 Method: The experimental animal used was male SD white rat with weight of 200 g. Blood sampling of the experimental animal was taken through orbital vein plexus. The animal was administered for the herbal composition of the present invention three (3) times a day for seven (7) days.

The experimental animals were divided into the control group and the study group. The control group animals were administered alcohol for one week. The study group animals were administered alcohol and concomitantly with 1 g/kg of the YGK herbal composition for one week. The rats' livers were tested for triglyceride and cholesterol level, lipid hyperoxidation, and glutathione peptide.

25 Results: After one (1) week of alcohol administration, triglyceride and cholesterol levels in the rats' liver were increased; lipid hyperoxidation and diminished glutathione peptide occurred in the control group. In contrast, in the study group, the fatty metamorphosis of the liver was inhibited. Also, the processes of lipid hyperoxidation and diminished glutathione peptide were inhibited in the study group animals.

30 Conclusion: The YGH herbal composition prevents accumulation of triglyceride and cholesterol levels in the liver which follows alcohol consumption, thus providing beneficiary effects on the liver functions.

Experiment 5.2. Analysis of Effect on Liver Cirrhosis in White Rats.

Purpose: The experiment was conducted to investigate the effect of the YGK herbal compositions on protein synthesis in white rats with liver cirrhosis.

Method:

5 The experimental animal used was male SD white rat with weight of 200 g. Blood sampling of the experimental animal was taken through orbital vein plexus. The animal was administered for the herbal composition of the present invention three (3) times a day for seven (7) days.

1. Induction of liver cirrhosis in the rats

10 The rats were injected subcutaneously on the back with 1 ml/200 g 50% chloroform (CCl₄) diluted in olive oil, for three (3) times a week for four (4) weeks. Liver biopsy was conducted through midline laparotomy. Most animals needed six (6) weeks of injection to induce liver cirrhosis. The injection dosage was adjusted each week in accordance to the weight of the rats.

15 Due to liver cirrhosis and partial liver resection, the serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) significantly increased in the rats.

2. Treating rats with the YGK herbal composition

The rats in the study group were subdivided into three (3) groups which were respectively administered the YGK herbal composition of the present invention for 500
20 mg/kg, 1000 mg/kg, or 2000 mg/kg.

Results:

1. ALT and AST Levels: after the treatment with the YGK herbal composition, the serum ALT and AST levels decreased in all three (3) different dosage treatment groups. The liver cirrhosis process was inhibited.

25 2. Hepatocyte Regeneration: after the administration of the herbal composition in three (3) different doses, the rates of liver regeneration in the rats were 19%, 30%, and 47%, respectively, higher than the rats with liver cirrhosis and partially resected livers which were not treated with the herbal composition, and the rates of liver regeneration in the treated rats were also 51%, 70%, and 92%, respectively, higher than the partially liver resected rats with
30 normal liver functions.

Conclusion:

The YGK herbal composition was effective in liver regeneration and had effectively inhibited the liver cirrhosis process.

EXAMPLE 6

Toxicity Study of the YGK Herbal Composition in Animals

Purpose:

5 The following experiment was conducted at the Toxicology Laboratory of the Institute of Labor, Health, and Occupational Disease of Heilungkiang Province in China to examine acute toxicity of the YGK herbal composition during intravenous injection in animals.

Methods:

10 Experimental animals were Japanese big-ear white rabbits obtained from the Animal Center of Haerbin Medical University in Haerbin, Heilungkiang Province, China. These rabbits were characterized by the obvious blood vessels on ears which facilitates the operation of injection during the experiments.

Ten (10) rabbits were obtained including six (6) males and four (4) females, each weighing between 1900 g to 3000 g.

15 The rabbits were randomly divided into two (2) groups, five rabbits in each group including two (2) females and three (3) males. The YGK herbal composition was intravenously injected into the rabbits through the veins on their ears at dosages of 10 g/kg and 15 g/kg, respectively, for two groups.

20 The concentration of injection fluid containing the herbal composition was about 1 g/ml. So the higher dosage group at 15 g/kg has a concentration of about 15 ml/kg, which could be calibrated as a sixty (60) kg-weighted adult who was treated by 900 ml of the herbal composition at a time.

25 The rabbits were observed for behaviour continuously for a period of two (2) weeks after intravenous injections. Observation was conducted hourly at day 1; during the following days, observation was conducted four-six (4-6) times per day.

At the end of the observation period, rabbits were sacrificed and dissected to examine the eyes, liver, lung, and spleen for adverse effects.

Results:

30 No abnormal behavior was observed of the rabbits during the observation period. The rabbits showed normal body weight increase during the period. After the sacrifice and dissection, inspection of the eyes, liver, lung, and spleen showed no extraordinary syndromes.

The results when compared to a general acute toxicity index were normal and no acute toxicity.

EXAMPLE 7

Effects of the YGK Herbal Composition on HIV in Cell Cultures

Purpose:

The following experiment was conducted in the Military Medical Research Institute in China to examine the effectiveness of the YGK herbal composition of the present invention in the form of intravenous product against HIV.

Methods:

MT4 cells were cultured in HIV-1 suspension liquid of 100 TCID₅₀ in a 96-hole culture plate. The culture condition was set at a temperature of 37°C and under 5% CO₂. The culture time was seven (7) days.

The YGK herbal composition of the present invention were added into the wells at various concentrations. The morphology of the MT4 cells were observed by conventional methods.

Results:

No pathological changes of MT4 cells were observed in wells where the YGK herbal composition was added to in adequate concentrations. The inhibition of the pathological changes of MT4 cells indicated that the YGK herbal composition had inhibitory effect on pathological changes of the cultured cells caused by HIV.

The effective concentration of the YGK herbal composition for inhibition of the pathological changes of MT4 cells was more than 12.5 mg/ml. To achieve a 50% of inhibition, the concentration of the YGK herbal composition was 25 mg/ml.

Conclusion:

The YGK herbal composition was effective in inhibiting pathological changes in cells caused by HIV-1 in vitro.

EXAMPLE 8

A Case Study on an HIV-Patient Treated With the YGK herbal Composition

Purpose:

The following clinical trial was conducted in the Infectious Disease Hospital in Shanghai, China to test the effectiveness of the herbal composition of the present invention in treating an HIV-infected patient.

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Methods:

A fifty-year Chinese male patient diagnosed with HIV infection complicated by herpes zoster was treated with anti-virus regimens by the combination of western medicine and the herbal composition of the present invention during hospital stay.

Results:

5 The patient was confirmed of HIV-infection by Rapid Agglutinin Assay. At the time of the initial diagnosis in August 1996, the patient showed no symptoms. Starting June 1, 1997, the patient quickly developed an herpetiform rash over the front of the left side of the check extending over the neck, the shoulder, and the upper left arm. The patient was then
10 admitted into the Hospital in June 24, 1997.

At the hospital, the result of the physical examination was normal except the skin rash. The pathology tests confirmed normal renal function. The functional tests of the liver showed a slightly increased levels of serum γ glutamyl transpeptidase and acetyl glucuronidase. Hepatitis viral tests showed negative for Hepatitis B virus and Hepatitis C
15 virus (HBV-DNA and HCV-RNA). However, Hepatitis G viral test showed positive for HGV-RNA. The immunological studies showed that the β -2 microglobulin level was 2.4-2.5 mg/ml.

During the hospital stay, haemoglobin and erythrocytes levels of the patient were slightly decreased, while the levels of the leukocyte and platelet were normal. Peripheral
20 blood lymphocytes counts showed that T4 cells were decreased to $2.76 \times 10^9/L$ (32.9%) and the ratio of T4/T8 cell was 1.16. Thus, the diagnosis is that the patient was with HIV infection complicated by herpes zoster.

During hospital stay, the patient had diarrhea and dry cough for a few days and was cured. In September, 1997, the patient showed HIV antibody positive by ELISA, and his T4
25 cells further decreased to 25.4% and the ratio of T4/T8 cells was inverted to 0.94. Then, T4 cells and the ratio of T4/T8 gradually increased after treatment with the YGK herbal composition and as tested in November 1997, his T4 cells were 40.7%, and the ratio of T4/T8 1.45. The skin rash gradually disappeared and completely recovered by the end of November.

Conclusion:

30 The YGK herbal composition was effective in reducing symptoms of the HIV-infected patient in a treatment regime together with western medicine.

EXAMPLE 9Clinical Trial on HIV-Infected Patients Treated With the YGK Herbal CompositionPurpose:

- The following clinical trial was conducted in De-Tang Hospital (National AIDS Therapy Center) in Beijing, China to test the effectiveness of the herbal composition of the present invention in treating HIV-infected patients.

Methods:

Five (5) HIV-infected patients were treated with the YGK herbal composition. The infection was confirmed by western blotting. The profile of the patients were as follows:

Patients	Sexuality	Age	History	Diagnosis
1	Male	32	2 years	AIDS (Stage IV)
2	Female	32	1 year	AIDS (Stage IV)
3	Male	31	1 year	AIDS (Stage III)
4	Male	25	0.5 year	AIDS (Stage II)
5	Male	17	3 weeks	HIV Infection

10

The patients were treated according to the following regimen:

- Five (5) ml injection fluid herbal composition of the present invention was dissolved in 250 ml 5% glucose solution. The solution was injected intravenously once per day for three (3) days. Then, the dosage was increased to 15 ml injection fluid in 250 ml 5% glucose solution, and the patients were injected intravenously once per day without uncomfortable reactions for three (3) months.

15

Additionally, patient #1 was treated with AZT + DDI therapy for ten (10) days before being treated with the YGK herbal composition; patient # 5 was treated with combination of interferon and the herbal composition.

20

Three (3) ml blood sample was taken from the patients each time before, during, and after the treatment and further tested for HIV.

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Results:

The HIV counts of the patients are as follows:

Patients	before treatment	1st month during treatment	2nd month during treatment	3rd month, at the end of treatment
1	1.9×10^4	1.7×10^5	6.3×10^3	1.5×10^4
2	1.5×10^4	6.3×10^3		3.8×10^2
3	7.3×10^3		3.2×10^3	
4	3.0×10^5	1.9×10^4		1.9×10^4
5	3.9×10^5	2.6×10^3	1.8×10^3	*

Note: the control level of HIV is 3,000.

- Based on the above table, all patients showed decreased HIV level and increased CD4 cells, except in patient # 5 who was also treated with interferon. Especially, patient # 2 had significant decrease of HIV; his CD4 counts also dropped from $285/\text{mm}^3$ to $510/\text{mm}^3$.

Conclusion:

The herbal composition of the present invention is effective in reducing HIV in serum in HIV-infected patients.

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EXAMPLE 10

Clinical Trial on HIV-Infected Patients Treated With
the YGK Herbal Composition In Russia

Purpose:

- The following experiment was conducted in Hospital in Siberia, Russia to examine the effectiveness of the YGK herbal composition of the present invention against HIV.

Methods:

- Five (5) HIV-infected patients were treated with the YGK herbal composition. The profile of the patients were as follows:

Patients	Sexuality	Age	History	Diagnosis
1	Female	23	2 years	AIDS (Phase A3), adenitis, hepatitis C, Syphilis, Citomegalo infection, Gonorrhea
2	Female	28	2 year	AIDS (Phase A3), adenitis, hepatitis B and C, Gerpec and Citomegalo infection, Gonorrhea, drug abuse

Patients	Sexuality	Age	History	Diagnosis
3	Male	35	1 year	AIDS (Phase B2), adenitis
4	Male	22	1 year	AIDS (Phase B2), adenitis, hepatitis C, drug abuse
5	Male	34	several months	AIDS (phase A3), adenitis, hepatitis B and C, 10% weight loss, drug abuse

The patients were treated with the herbal composition of the present invention. Samples were taken from the patients each time before, during, and after the treatment and further tested for CD4 cells.

5 Results:

The CD4 cells counts of the patients are as follows:

Patients	before treatment	2nd month during treatment	5th month, at the end of treatment
1	477	641	849
2	740	1140	705
3	421	...	527
4	440	490	669
5	625	...	814

Note: the normal level of CD4 cell count is about 500.

During the treatment process, all patients had positive response except some minor side effects. The symptoms of the patients were improved after one month of treatment including alleviation of weakness, depression, and stegnosis. The abdominal region pain and uncomfortable feeling also disappeared. Patients # 4 and # 5 had 5 kg increase of body weight after three (3) months of treatment. Patients #2 and #4 were disintoxicated. The biological marker of the liver showed normal after all patients after the treatment.

Based on the above table, all patients showed increased CD4 cell counts except patient #2.

Conclusion:

The herbal composition of the present invention is effective in reducing symptoms in AIDS patients.

We claim:

1. A herbal pharmaceutical composition for treating patients with liver disease and/or HIV comprising:
 - an entire plant of *Herba Hedyotidis diffusae* (diffuse hedyotis);
 - 5 a dried rhizome of *Rhizoma Bistortae* (bistort rhizome);
 - a dried rhizome of *Rhizoma Polygoni Cuspidati* (giant knotweed rhizome); and
 - a dried ripe fruit of *Fructus Schisandrae* (Chinese magnoliavine fruit).
2. The herbal pharmaceutical composition according to claim 1, further
10 comprising:
 - a dried rhizome of *Rhizoma Menispermis* (Asiatic moonseed rhizome);
 - a dried root of *Radix Scutellariae* (baical skullcap root);
 - bovine biliary powder;
 - a dried root tuber of *Radix Curcumae* (tumeric root-tuber);
 - 15 a dried ripe fruit of *Fructus Crataegi* (hawthorn fruit); and
 - a dried root of *Radix Notoginseng* (sanqi).
3. The herbal pharmaceutical composition according to claim 2, further
comprising:
 - 20 a dried ripe fruit of *Fructus Lycii* (barbary wolfberry fruit);
 - a steamed and dried root of *Radix Ginseng Rubra* (red ginseng);
 - a dried root of *Radix Scrophulariae* (figwort root);
 - a dried root of *Radix Angelicae sinensis* (Chinese angelica); and
 - a dried root of *Radix Astragali* (milkvetch root).
- 25 4. The herbal pharmaceutical composition according to claim 1, wherein said diffuse hedyotis, said bistort rhizome, said giant knotweed rhizome, and said Chinese magnoliavine fruit are in a weight ratio of about 3: 3: 1: 2.
- 30 5. The herbal pharmaceutical composition according to claim 2, wherein said diffuse hedyotis, said bistort rhizome, said giant knotweed rhizome, said Chinese magnoliavine fruit, said asiatic moonseed rhizome, said baical skullcap root, said bovine biliary powder, said

tumeric root-tuber, said hawthorn fruit, and said sanqi are in a weight ratio of about 3: 3: 1: 2: 1: 1: 0.1: 1: 2: 1.

5 6. The herbal pharmaceutical composition according to claim 3, wherein said diffuse hedyotis, said bistort rhizome, said giant knotweed rhizome, said Chinese magnoliavine fruit, said asiatic moonseed rhizome, said baical skullcap root, said bovine biliary powder, said tumeric root-tuber, said hawthorn fruit, said sanqi, said barbary wolfberry fruit, said red ginseng, said figwort root, said Chinese angelica, and said milkvetch root are in a weight ratio of about 3: 3: 1: 2: 1: 1: 0.1: 1: 2: 1: 3: 1: 2: 1: 3.

10

7. The herbal pharmaceutical composition according to claim 1, wherein said liver disease comprises viral hepatitis, alcoholic or fatty liver, liver cirrhosis, and liver cancer.

8. The herbal pharmaceutical composition according to claim 7, wherein said viral hepatitis is one selected from the group consisting of hepatitis A (HAV), hepatitis B (HBV),
15 hepatitis C (HCV), and hepatitis E (HEV).

9. A method for treating patients with liver disease comprising administering said herbal pharmaceutical composition according to claim 1 to patients with liver disease.

20

10. A method for treating patients with liver disease comprising administering said herbal pharmaceutical composition according to claim 2 to patients with liver disease.

11. A method for treating patients with liver disease comprising administering said herbal pharmaceutical composition according to claim 3 to patients with liver disease.

25

12. A method for treating patients with HIV comprising administering said herbal pharmaceutical composition according to claim 1 to patients with HIV.

13. A method for treating patients with liver disease comprising administering said
30 herbal pharmaceutical composition according to claim 2 to patients with HIV.

14. A method for treating patients with liver disease comprising administering said herbal pharmaceutical composition according to claim 3 to patients with HIV.

15. A method for preparing the herbal pharmaceutical composition according to claim 1, comprising:

5 grinding and mixing the entire plant of diffuse hedyotis, the dried rhizome of bistort rhizome, the dried rhizome of giant knotweed rhizome, and the dried ripe fruit of Chinese magnoliavine fruit to form a herbal mixture;

boiling said herbal mixture in water;

filtering said boiled herbal mixture to separate said herbal mixture from a herbal solution containing herbal extracts; and

10 concentrating said filtered herbal solution containing said herbal extracts.

16. The method according to claim 15, further comprising:

spray-drying and granulating said concentrated herbal solution to form herbal granules.

15

17. The method according to claim 15, wherein said herbal mixture is first boiled in water for 2 hours and then, after cooling down, is boiled again for 1.5 hours.

18. The method according to claim 15, wherein said filtered herbal solution is
20 concentrated from about 1.4 to 1 by volume.

19. The method according to claim 16, wherein said herbal granules are encapsulated.

20. A method for preparing the pharmaceutical composition according to claim 2, comprising:

25 grinding and mixing the entire plant of diffuse hedyotis, the dried rhizome of bistort rhizome, the dried rhizome of giant knotweed rhizome, the dried ripe fruit of Chinese magnoliavine fruit, said asiatic moonseed rhizome, said baical skullcap root, said bovine biliary powder, said tumeric root-tuber, said hawthorn fruit, and said sanqi to form a herbal mixture;

30 boiling said herbal mixture in water;

filtering said boiled herbal mixture to separate said herbal mixture from a filtered herbal solution; and

concentrating said filtered herbal solution containing said herbal extracts.

21. The method according to claim 20, further comprising:
spray-drying and granulating said concentrated herbal solution to form herbal
granules.

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22. The method according to claim 20, wherein said filtered herbal solution is
concentrated from about 1.4 to 1 by volume.

23. The method according to claim 21, wherein said herbal granules are encapsulated.

10

24. A method for preparing the pharmaceutical composition according to claim 3,
comprising:

grinding and mixing the entire plant of diffuse hedyotis, the dried rhizome of bistort
rhizome, the dried rhizome of giant knotweed rhizome, the dried ripe fruit of Chinese
magnoliavine fruit, said asiatic moonseed rhizome, said baical skullcap root, said bovine
biliary powder, said tumeric root-tuber, said hawthorn fruit, said sanqi, said barbary
wolfberry fruit, said red ginseng, said figwort root, Chinese angelica; and said milkvetch root
to form a herbal mixture;

boiling said herbal mixture in water;
filtering said boiled herbal mixture to separate said herbal mixture from a herbal
solution containing herbal extracts; and
concentrating said filtered herbal solution containing herbal extracts.

25. The method according to claim 24, further comprising:
spray-drying and granulating said concentrated herbal solution to form herbal
granules.

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26. The method according to claim 24, wherein said filtered herbal solution is
concentrated from about 1.4 to 1 by volume.

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27. The method according to claim 25, wherein said herbal granules are encapsulated.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 35/78

US CL : 424/725, 728, 773, 777

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/725, 728, 773, 777

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,837,257 A (TSAI et al.) 17 November 1998 (17.11.98), see entire document.	1, 4, 7-9, 12, 15-19
Y	CN 1,151,312 A (JIANG) 11 June 1997 (11.06.97), DWPI Abstract.	1, 4, 7-9, 12, 15-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents.	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

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